

University of Dundee

## **A Type 1 Diabetes Genetic Risk Score Can Identify Patients With GAD65 Autoantibody-Positive Type 2 Diabetes Who Rapidly Progress to Insulin Therapy**

Grubb, Anita L.; McDonald, Timothy J.; Rutters, Femke; Donnelly, Louise; Hattersley, Andrew T.; Oram, Richard A.

*Published in:*  
Diabetes Care

*DOI:*  
[10.2337/dc18-0431](https://doi.org/10.2337/dc18-0431)

*Publication date:*  
2019

*Document Version*  
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

### *Citation for published version (APA):*

Grubb, A. L., McDonald, T. J., Rutters, F., Donnelly, L., Hattersley, A. T., Oram, R. A., Palmer, C., van der Heijden, A. A., Carr, F., Elders, P. J. M., Weedon, M., Slieker, R. C., 't Hart, L. M., Pearson, E., Shields, B. M., & Jones, A. G. (2019). A Type 1 Diabetes Genetic Risk Score Can Identify Patients With GAD65 Autoantibody-Positive Type 2 Diabetes Who Rapidly Progress to Insulin Therapy. *Diabetes Care*, 42(2), 208-214. <https://doi.org/10.2337/dc18-0431>

### **General rights**

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

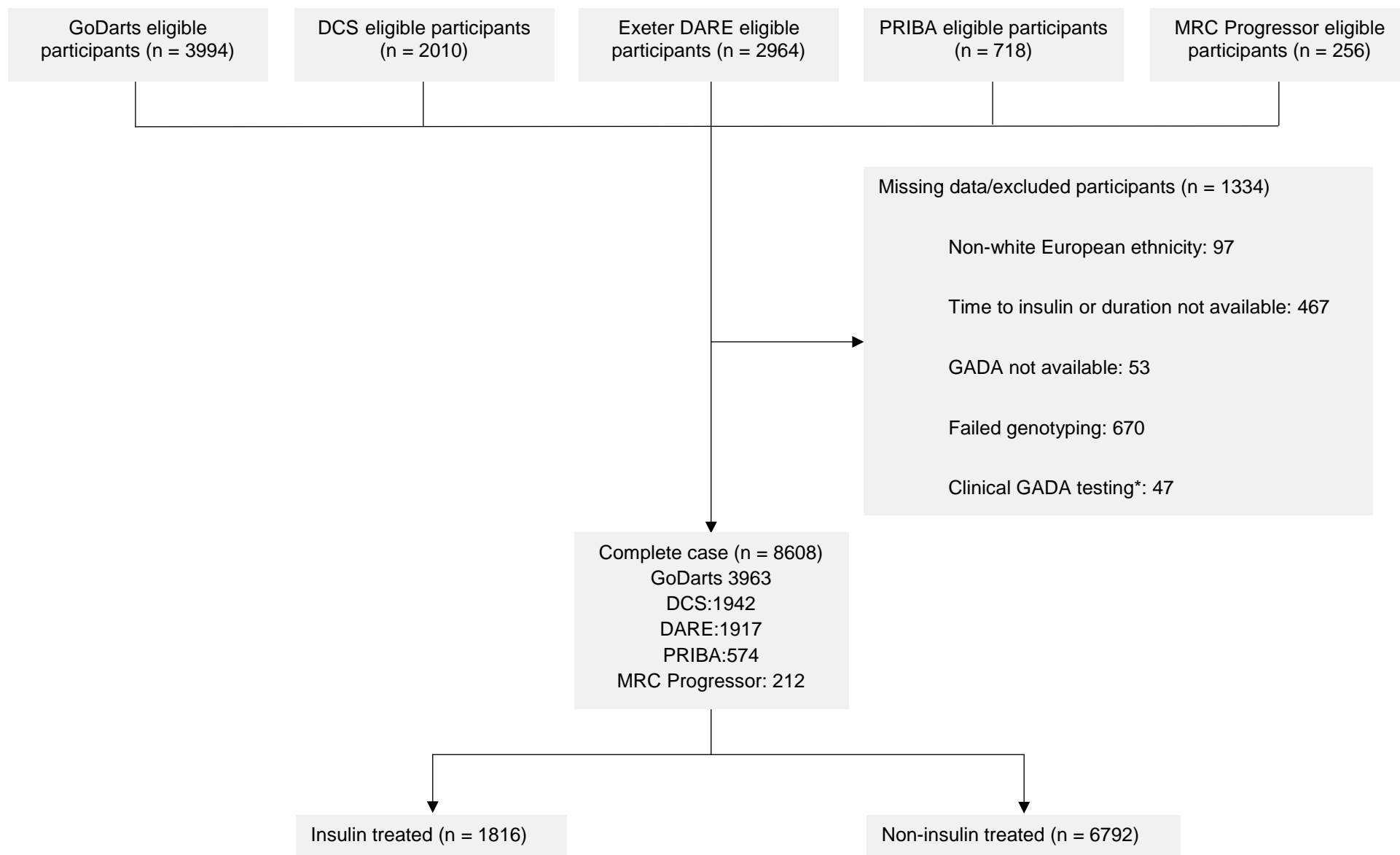
### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

## Supplementary material

	GoDarts	DCS	DARE	PRIBA	MRC Progressor
Included participants	3963	1942	1917	574	212
Data collection period	From 1998	From 1998	2007 to 2017	2011 to 2013	2013 to 2015
Study design	Longitudinal	Longitudinal	Cross sectional	Longitudinal	Cross sectional
Setting	Primary and secondary care in Tayside, Scotland	Primary and secondary care in West-Friesland, Netherlands	Primary and secondary care in eight diabetes research regions, England and retinal screening clinics.	Primary and secondary care in South West England	Primary and secondary care in Exeter, Dundee and Oxford, England
Inclusion criteria	Clinical diagnosis of type 2 diabetes.	Clinical diagnosis of type 2 diabetes.	Clinical diagnosis of diabetes (any type).	Clinical diagnosis of type 2 diabetes. Clinician determined requirement for DPP-IV inhibitor or GLP-1 analogue (HbA1C >7.5%)	Clinical diagnosis of type 2 diabetes non-insulin treated within 6 months of diagnosis. Participants were selected on the basis of rapid or slow progression to insulin therapy (<7, >7 years). Age 18-90 inclusive.
Data collection	Clinical measurements and blood collected at initial visit. Follow up clinical data constantly updated using electronic medical record linkage.	Clinical measurements collected at initial visit, and repeated annually. Blood collected at one of the annual visits. Additional health data collected using electronic medical record linkage.	Clinical measurements and blood sample collected at visit. Ongoing biochemical data collected from pathology laboratories.	Clinical measurements and blood taken at initial visit. Follow up clinical measurements and blood collected at three and six months.	Clinical measures and fasting blood sample taken at visit.

Supplementary Table 1: Cohort recruitment and data collection methods summary



Supplementary Figure { SEQ Supplementary\_Figure \\* ARABIC }: Participant flow diagram \* identified through search of electronic laboratory records.

SNP	Gene	Odds Ratio	Weight	Effect Allele
rs2187668, rs7454108	DR3/DR4	48.18	3.87	
	DR3/DR3	21.12	3.05	
	DR4/DR4	21.98	3.09	
	DR4/X	7.03	1.95	
	DR3/X	4.53	1.51	
rs1264813	HLA_A_24	1.54	0.43	T
rs2395029	HLA_B_5701	2.5	0.92	T
rs3129889	HLA_DRB1_15	14.88	2.70	A
rs2476601	PTPN22	1.96	0.67	A
rs689	INS	1.75	0.56	T
rs12722495	IL2RA	1.58	0.46	T
rs2292239	ERBB3	1.35	0.30	T
rs10509540	C10orf59	1.33	0.29	T
rs4948088	COBL	1.3	0.26	C
rs7202877		1.28	0.25	G
rs12708716	CLEC16A	1.23	0.21	A
rs3087243	CTLA4	1.22	0.20	G
rs1893217	PTPN2	1.2	0.18	G
rs11594656	IL2RA	1.19	0.17	T
rs3024505	IL10	1.19	0.17	G
rs9388489	C6orf173	1.17	0.16	G
rs1465788		1.16	0.15	C
rs1990760	IFIH1	1.16	0.15	T
rs3825932	CTSH	1.16	0.15	C
rs425105		1.16	0.15	T
rs763361	CD226	1.16	0.15	T
rs4788084	IL27	1.16	0.15	C
rs17574546		1.14	0.13	C
rs11755527	BACH2	1.13	0.12	G
rs3788013	UBASH3A	1.13	0.12	A
rs2069762	IL2	1.12	0.11	A
rs2281808		1.11	0.10	C
rs5753037		1.1	0.10	T

Supplementary Table 2: Type 1 diabetes SNPs included in the genetic risk score with weights. Effect allele is the risk increasing allele on the positive strand.

SNP	Gene	Odds Ratio	Weight	Effect Allele
rs2187668, rs7454108	DR3/DR4	48.18	3.87	
	DR3/DR3	21.12	3.05	
	DR4/DR4	21.98	3.09	
	DR4/X	7.03	1.95	
	DR3/X	4.53	1.51	
rs1264813	HLA_A_24	1.54	0.43	T
rs2395029	HLA_B_5701	2.5	0.92	T
rs3129889	HLA_DRB1_15	14.88	2.70	A
rs2476601	PTPN22	1.96	0.67	A
rs689	INS	1.75	0.56	T
rs12722495	IL2RA	1.58	0.46	T
rs2292239	ERBB3	1.35	0.30	T
rs10509540	C10orf59	1.33	0.29	T

Supplementary Table 3: Type 1 diabetes SNPs included in the 10 SNP T1D GRS

	<i>DCS Hoorn</i> (n = 1 942)	<i>GoDarts</i> (n = 3 963)	<i>Exeter studies</i> (n= 2 702 )	<i>p-value</i>
Sex (% Male)	54.6%	54.8%	60.2%	<0.001
Age at diagnosis (years)	60 (53, 67)	61 (54, 68)	59 (50, 67)	<0.001
BMI (kg/m <sup>2</sup> )*	29.5 (26.8, 33.2)	30.4 (27.2, 34.6)	31.1 (27.5, 35.7)	<0.001
Duration of diabetes (years) †	7.1 (4.3, 11.0)	12.8 (10.3, 15.7)	7.0 (3.0, 12.3)	<0.001
Duration of diabetes (years) at GADA	8.2 (5.3, 12.2)	5.1 (2.7, 8.0)	7.0 (3.0, 12.0)	<0.001
Insulin treated within 5 years (%)‡	5.8	7.4	10.2	<0.001
HbA1c (%)†	6.5 (6.1, 7.1)	7.2 (6.5, 8.2)	7.3 (6.6, 8.4)	<0.001
HbA1c (mmol/mol) †	48 (43, 54)	55 (48, 66)	56 (49, 68)	<0.001
GADA Positive (%)	2.2%	3.9%	3.1%	<0.001
T1D GRS centile§	4.7 (0.9, 16.1)	3.9 (0.5, 15.9)	4.2 (0.7, 16.3)	<0.001

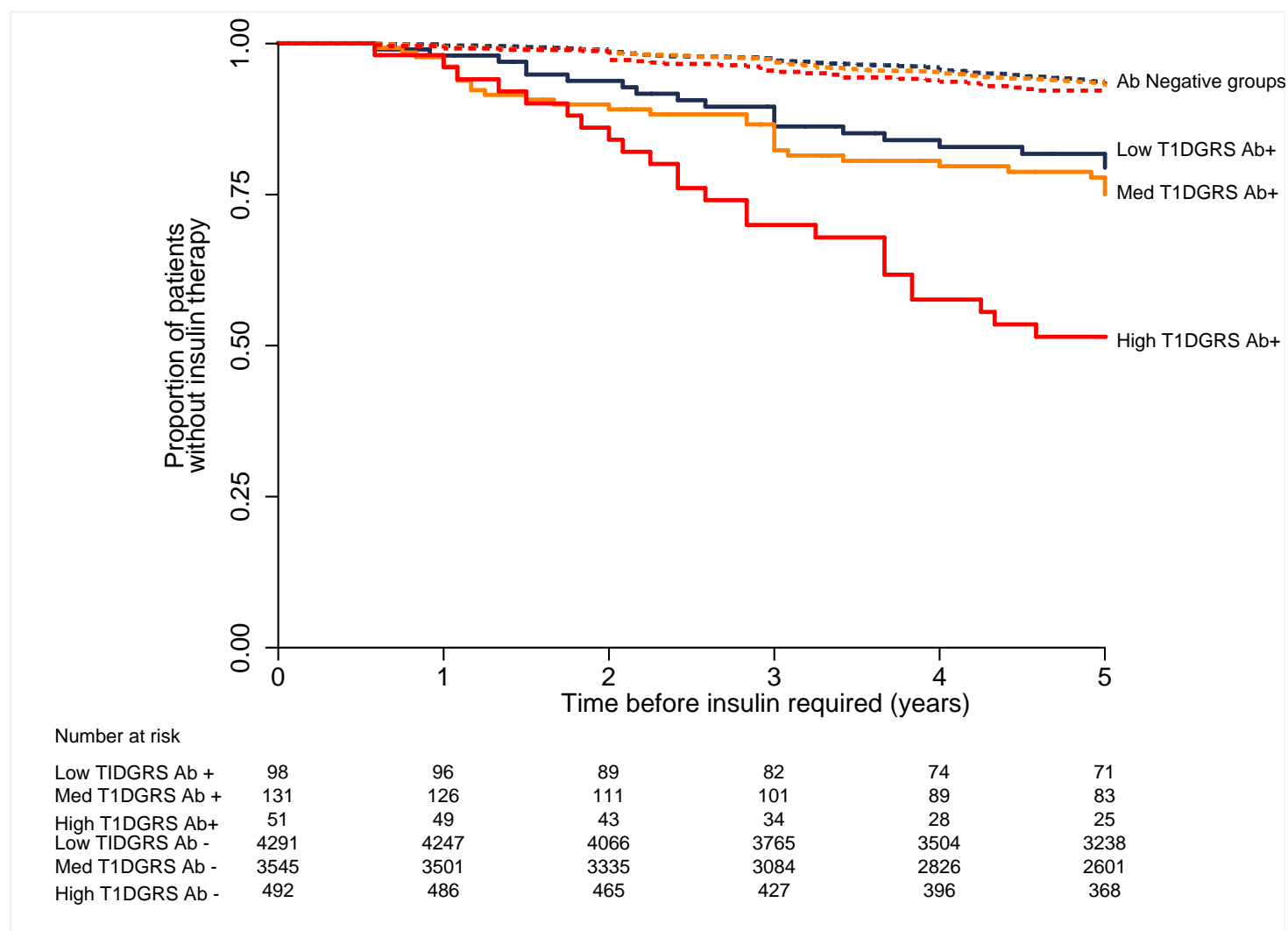
Supplementary Table 4: Participant characteristics stratified by cohort. Median (IQR) or %  
Kruskal-Wallis used for comparison testing continuous variables, chi-square for categorical variables  
Exeter cohorts are shown combined due to low numbers in PRIBA and MRC Progressor

\* Closest to diagnosis

† At latest follow up

‡ Percentage of participants observed for at least five years

§ Centile of participants with type 1 diabetes from the Wellcome trust case control consortium.



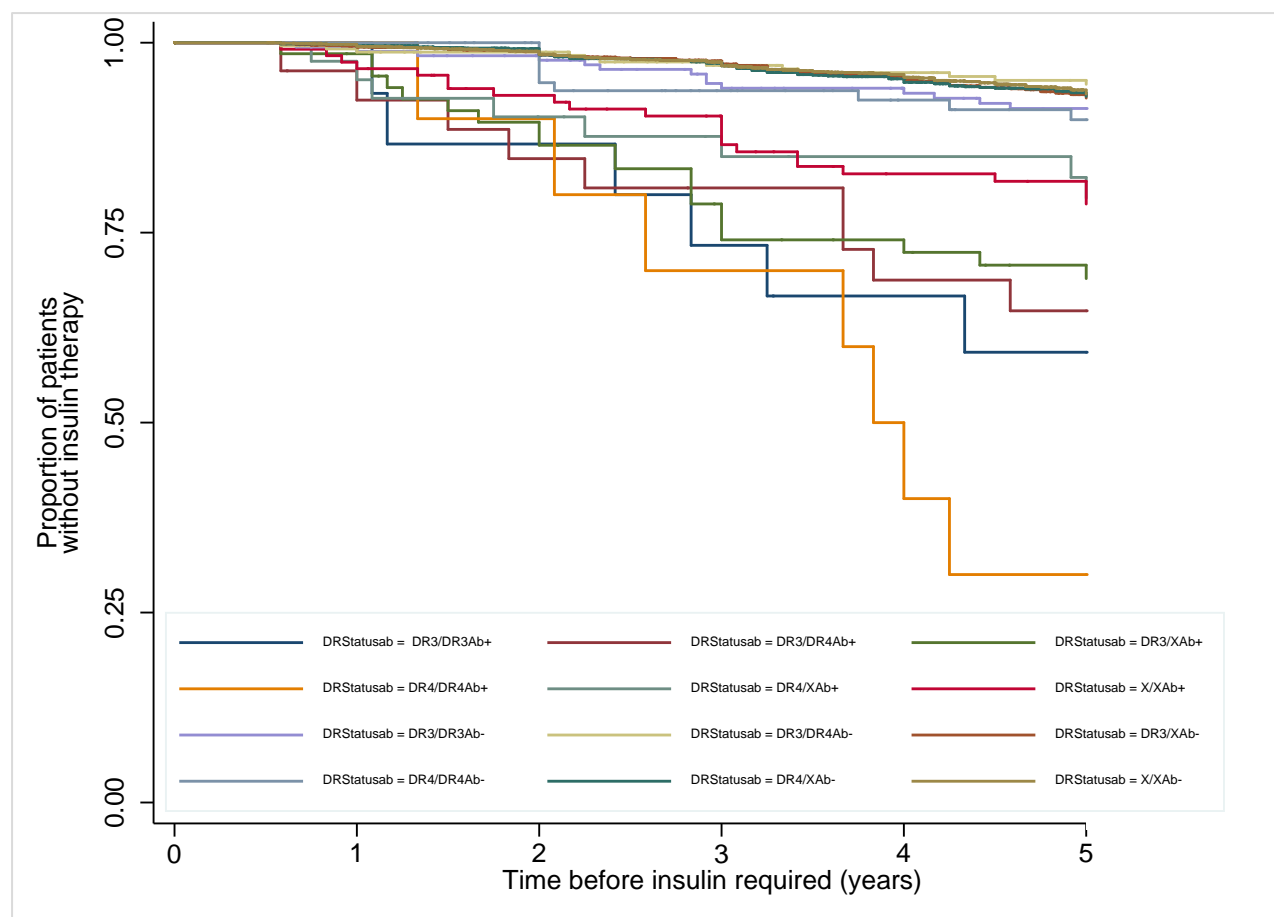
Supplementary Figure 2: Kaplan-Meier plot of probability of requiring insulin therapy by risk group using 10 SNP T1D GRS. Solid lines represent GADA positive groups, dashed lines represent GADA negative groups. Blue = low T1D GRS centile, orange = medium T1D GRS centile, red = high T1D GRS centile.

Variable	Hazard Ratio (95% CI)	p value
GADA Negative	1	
GADA Positive	3.70 (2.74, 4.99)	<0.001
GADA Negative:10 SNP T1D GRS (per 1 SD change in T1D GRS)	1.04 (0.96, 1.14)	>0.1
GADA Positive:10 SNP T1D GRS (per 1 SD change in T1D GRS)	1.34 (1.05, 1.71)	0.02
Age at diagnosis (per 1 year)	0.97 (0.96, 0.98)	<0.001
BMI (per kg/m <sup>2</sup> unit)	1.00 (0.98, 1.01)	>0.1

Supplementary Table 5: Hazard ratios from Cox proportional regression model for time to insulin censored at 5 years (10 SNP T1D GRS)

\* Closest to diagnosis

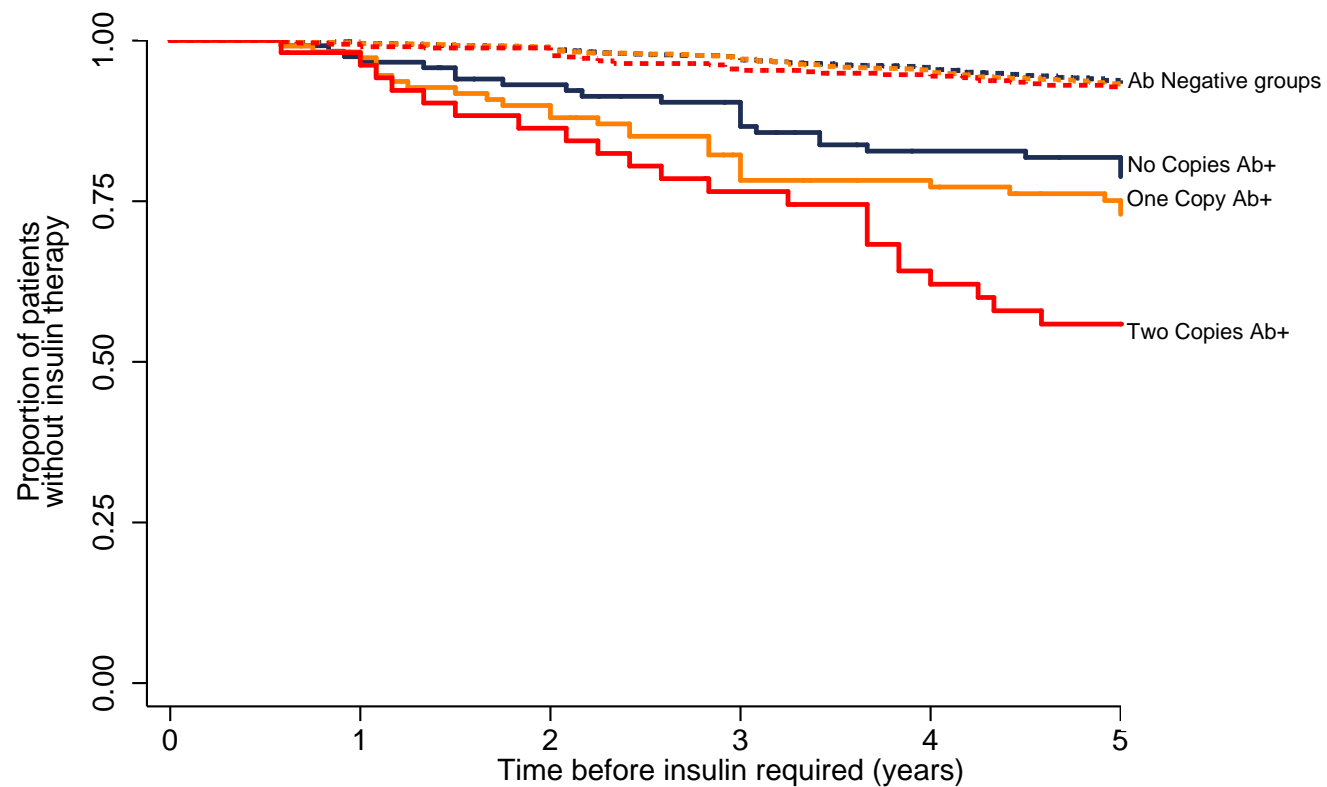




Number at risk

No Copies Ab+	15	15	13	11	9	8
One Copy Ab+	27	25	22	20	17	16
Two Copies Ab+	69	67	59	50	45	40
No Copies Ab-	10	10	9	7	5	3
One Copy Ab-	42	40	36	33	31	30
Two Copies Ab-	117	114	104	96	84	82

Supplementary Figure 3: Kaplan-Meier plot of probability of requiring insulin therapy by risk group using HLA DR3/DR4 alleles.



Number at risk

NoCopies Ab+	117	114	104	96	84	82
OneCopy Ab +	111	107	95	83	76	70
Two Copies Ab+	52	50	44	38	31	27
NoCopies Ab -	4617	4565	4355	4038	3740	3456
OneCopies Ab -	3186	3152	3016	2791	2574	2365
Two Copies Ab -	524	516	494	446	411	385

Supplementary Figure 4: Kaplan-Meier plot of probability of requiring insulin therapy by risk group using HLA DR3/DR4 alleles. Solid lines represent GADA positive groups, dashed lines represent GADA negative groups. Blue = No DR3/DR4 copies, orange = one DR3/DR4 copy, red = two DR3/DR4 copies.